Toxin types, toxicokinetics and toxicodynamics

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Cyanobacteria produce a wide array of bioactive secondary metabolites, some which are toxic. Those toxic to mammals include the microcystins, cylindrospermopsins, saxitoxins, nodularins, anatoxin-a, homoanatoxin-a, and anatoxin-a(s). Microcystins (MCs) are a group of at least 80 variants based on a cyclic heptapeptide structure. All toxic variants contain a unique hydrophobic amino acid, 3-amino-9-methoxy-10-phenyl-2,6,8-trimethyl-deca-4(E),6(E)-dienoic acid (ADDA), which is necessary for toxin binding to the active site of protein phosphatases 1 and 2A, and most contain dehydroalanine, which can undergo covalent linkage to a cysteinyl sulphur on the phosphatase. The type-compound, MC-LR, which has leucine and arginine at two hypervariable positions in the ring structure, has a LD_{50} (ip, mice) of 60 µg/kg. Substitution of other amino acids at these sites, or methylation of residues at other sites, can reduce potency. Because uptake is via specific organic anion transport proteins, MCs exhibit a predominantly hepatic organotropism, although enteric and even dermal effects have been demonstrated in certain circumstances. The primary acute effect of MC toxicity is disruption of the hepatocellular cytoskeleton, which causes loss of cell-cell contacts and intra-hepatic haemorrhage. Death is due to hypovolemic shock. Chronic exposure has been shown to enhance the growth of hepatic and colonic pre-cancerous lesions, suggesting that the MCs may act as tumour promoters. Human intoxication via dialysis (possibly in combination with cylindrospermopsin) resulted in visual disturbances, nausea and vomiting and death from liver failure.

The cylindrospermopsins (CYNs) are alkaloids comprised of a tricyclic guanidino moiety linked via a hydroxylated bridging carbon (C7) to uracil. Structural variants are 7-epi-CYN and 7-deoxy-CYN, the latter having perhaps slightly lower potency than the 7-hydroxylated variants. LD_{50} of CYN indicates a delayed toxicity (2.0 mg/kg, ip mouse, after 24 hrs but 0.2 mg/kg after 5 days). The primary acute effect appears to be irreversible protein synthesis inhibition although genotoxic effects have also been demonstrated. There is some evidence of carcinogenicity but more work is required to confirm this. Effects of poisoning in humans include hepatoenteritis and renal insufficiency.

The saxitoxins have been extensively studied due to their involvement in paralytic shellfish poisoning where toxigenic marine dinoflagellates are consumed by shellfish, which concentrate the toxins and can deliver toxic quantities to consumers of the shellfish. Saxitoxins are alkaloids based on a 3,4,6-trialkyl tetrahydropurine skeleton which can be further carbamylated, sulphated or N-sulphocarbamylated to produce a range of perhaps 30 analogues, some of which are found only in freshwater cyanobacteria. These toxins are potent sodium channel blockers (saxitoxin LD_{50}, ip mouse, is 10 µg/kg), causing numbness, paralysis and death by respiratory arrest. Toxicological studies to date have assumed an acute exposure paradigm rather than sub-chronic low-dose as might be expected from drinking water. Long-term effects from sub-lethal acute exposure have not been reported. Neuro-developmental effects have been demonstrated in fish but have not been studied in mammals.

Nodularins are hepatotoxic cyclic peptides of similar structure to the microcystins except that they are composed of 5 amino acids rather than 7. Variants due to substitution of arginine with homoarginine or valine have been described, but these appear to be relatively rare. ADDA is still present but dehydroalanine is replaced by N-methyl-dehydrobutyrine. The smaller ring size prevents this latter moiety from coordinating with the phosphatase cysteine, and so nodularin does not bind covalently. However, due to the high affinity of ADDA for the active site, this lack of covalent binding does not affect toxin potency, which is similar to that of microcystin-LR.

Anatoxin-a (2-acetyl-9-azabicyclo(4-2-1)non-2-ene) and homoanatoxin-a (propionyl residue replaces acetyl at C2) are nicotinic acetylcholine receptor agonists. Residence of these toxins at post-synaptic cholinergic receptors results in nerve depolarisation. Typical symptoms in mice are loss of muscle coordination, gasping, convulsions and death within minutes from respiratory arrest. The LD_{50} is 200 µg/kg. Anatoxin-a(s) is a phosphorylated cyclic N-hydroxyguanine. It is a potent acetylcholinesterase inhibitor with a LD_{50} (ip, mouse) of 20 µg/kg.

New toxins, toxin analogues, and toxicity unexplained by known toxins, continue to be reported.